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SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
08/933,821	09/19/97	GODOWSKI P	P1130

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EXAMINER	
KAUFMAN, C	
ART UNIT	PAPER NUMBER
1646	9

DATE MAILED: 06/08/98

Please find below a communication from the EXAMINER in charge of this application.

Commissioner of Patents

Office Action Summary	Application No. 08/933,821	Applicant(s) Godowski et al.
	Examiner Claire M. Kaufman	Group Art Unit 1646

☒ Responsive to communication(s) filed on *Mar 16, 1998* .

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-15* is/are pending in the application.

Of the above, claim(s) *1-7 and 9-12* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *8 and 13-15* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☒ Claims *1-15* are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☒ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *5,6*

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. The amendment filed 3/16/98 has been entered.

Election/Restriction

2. Applicant's election with traverse of Group IV in Paper No. 8 is acknowledged. The traversal is on the ground(s) that: there is not a serious burden of search; all nucleic acids or polypeptides are members of one respective Markush group; up to ten nucleotide sequences should be examined in one application; and, different fields of search are not required. This is not found persuasive for several reasons. A serious burden of search is required since the fields of search are not overlapping because a series of distinct nucleic acids and distinct polypeptides are claimed. The claims as currently written constitute an improper Markush group because each nucleic acid or polypeptide is a distinct ligand, not "alternatively usable substances" (MPEP 803.02). One would not expect based on the prior art or disclosure that each ligand binds the same receptor with a comparable affinity and efficacy. Further, there is no disclosure that each ligand even binds the same TIE receptor (at least two distinct receptors are disclosed in the prior art). Because the claims are not proper Markush groups, an election of species is not indicated. As to "unity of invention" in a Markush group, unity exists when compounds (1) share a common utility--which has not been disclosed in the current specification since it is not known if the ligands bind the same receptor, and if they do bind the same receptor, by virtue of their expected different binding affinities for the receptor, would not be equivalent and would be used differently for interactions with the receptor; and (2) share a substantial structural feature disclosed as essential to that utility-- which likewise has not been shown even though applicants point to shared amino acid identity of 64-74% in the "fibrinogen domain" (which has not been assigned a specific function), because the amino acid sequence of NL1 and NL5 share only about 58% identity, NL1 and NL8 about 40%, NL5 and NL8 about 40%, and the nucleic acid sequence (including disclosed non-coding sequence) of NL1 and NL5 share about 10% identity, NL1 and NL8 about

12%, and NL5 and NL8 about 5% identity. One finds such sequence similarity among families of proteins including both ligands and receptors, however each protein is distinct because it is structurally and functionally distinct from another. Additionally, applicants have not taught any structural feature essential to the disclosed utility which is common to the claimed proteins. As to the requirement for searching up to 10 nucleic acid sequences, it is maintained that this concession is made for cases in which the claimed nucleic acids have no known function other than as hybridization probes (*e.g.*, expressed sequence tags). Also, it was designed to benefit applications which recite thousands of individual nucleotide sequences (Official Gazette, 1187 OG 62). Whether or not the claims specify that the claimed nucleic acids are TIE receptor ligands, the specification discloses them as such. Therefore, the search extends beyond the nucleic acid sequence into the art related to tyrosine kinase receptors and ligands. Applicants may petition pursuant to 37 CFR 1.181 for examination of additional nucleotide sequences by providing evidence that the different nucleotide sequences do not cover independent and distinct inventions. As previously stated, different fields of search are required because each nucleic acid and protein has a different sequence. Since each protein is distinct, an antibody specifically binding a specific protein is distinct from an antibody specifically binding to a different distinct protein. The searching for either the polypeptide or nucleic acid is a different search than for the antibody.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-7 will be examined as they relate to NL1.

Drawings

3. Figures 1A, 1B, and 2-7 of the instant application are each presented on two or three separate panels. 37 C.F.R. § 1.84 (u)(1) states that when partial views of a drawing which are intended to form one complete view, whether contained on one or several sheets, must be identified by the same number followed by a capital letter. The two sheets, must be identified by

the same number followed by a capital letter. The two sheets of drawing which are labeled "Figure 1A" in the instant specification should be renumbered "Figures 1A and 1B", and Figure 1B should be renumbered "Figures 1C-1D". Applicant is reminded that once the drawings are changed to meet the separate numbering requirement of 37 C.F.R. § 1.84 (u)(1), Applicant is required to change the Brief Description of the Drawings and the rest of the specification accordingly.

Specification

4. The disclosure is objected to because of the following informalities: on page 2, line 12, "TAI-2" appears to be a mistake; on p. 51, line 27, "associate1d" is incorrect; and p. 52, lines 14 and 15, and page 51, lines 18-19, have blanks where the date and number of the ATCC deposit should appear.

Appropriate correction is required.

5. Applicants are advised that the ATCC has moved from Rockville, MD to Manassas, VA, effective March 23, 1998. The correct address is now:

American Type Culture Collection
10801 University Boulevard
Manassas, VA 20110-2209

The specification should be amended at page 51, 52, and 65 to reflect the correct address for the ATCC.

Claim Objections

6. Claims 8 and 13-15 are objected to being drawn to non-elected inventions (NL5, NL8, or an antibody accoridng to claim 9).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 8 and 13-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polypeptide comprising the sequence of SEQ ID NO: 2 or having the sequence of amino acids 270-493 of SEQ ID NO:2, does not reasonably provide enablement for a polypeptide which shares at least 90% identity with amino acids 270-493 (the fibrinogen domain) of SEQ ID NO:2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction of guidance by the inventor, and 8) quantity of experimentation need to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The current claims are drawn to a nucleic acid encoding a polypeptide that is 90% identical to the C-terminal 46% (*i.e.*, the "fibrinogen domain") of the polypeptide described as NL1 (paragraph bridging pages 5-6). In other words, there is no structural limitation on the N-terminal half of the polypeptide. There is no functional limitation in the claims. The specification suggests that based on the sequence similarity between NL1 and the prior art hTL-1 and hTL-2 TIE2 receptor ligands (23% identity, p. 52, line 14), NL1 is a TIE ligand. The "fibrinogen domain" is 63-74% identical to the corresponding domain of other disclosed NL ligands (p. 53,

last paragraph). No function has been assigned to the fibrinogen domain. Davis et al. (7), who isolated the TIE2 receptor ligand angiopoietin-1 (also known as hTL1), state (p. 1166, col. 1, second paragraph) that,

> Numerous proteins are known to posses domains resembling the C-terminal domain of fibrinogen, but in most cases little is known about the functions of these proteins. It is noteworthy that all known examples of this type of protein have the fibrinogen-like domain at the C-terminus and that most are accompanied by N-terminal domains that have coiled-coil structures...; it is not known whether these shared structures form the basis for some common functional theme.

What part of NL1 is responsible for binding a TIE receptor is not disclosed. With what affinity one could expect binding to occur is not disclosed. To which TIE receptor (TIE1, TIE2, or an as of yet unidentified TIE receptor) NL1 binds is not disclosed. No ligand for the TIE1 receptor has been identified in the prior art. It is acknowledged that the relative skill of the artisan in the receptor/ligand molecular biology art is high. The amount of predictability about receptor binding by a ligand based solely on amino acid sequence is low since so few TIE receptor ligands are known. On page 10, lines 15-16, the specification states that "Since it is often difficult to predict in advance the characteristics of a variant TIE ligand, it will be appreciated that some screening will be needed to select the optimum variant." However, there is not disclosure of what constitutes an "optimum variant". Not only is there no disclosure of which TIE receptor NL1 binds to, there is no information about which amino acids or regions are required for specific binding at a site that either leads to or blocks signal transduction. The disclosure has not provided information that would allow the skilled artisan to predict if a polypeptide encompassed the claims would reasonably be expected to function as a ligand for a TIE receptor, or if it did not, what it could be used for. Since the only structural limitation of the claimed polypeptide is that the amino acid sequence comprise a portion which is 90% identical to amino acid from about residue 270 to about 493 of SEQ ID NO:2, the region outside that portion need have no structural relationship to NL1, and since 1/10 amino acids in the portion could be different, whatever function the fibrinogen domain had in the disclosed NL1 would not be expected to be retained. For example,

one would not reasonably expect that an antibody made to that modified region would specifically bind naturally occurring NL1 because of differences in 3-dimensional structure and amino acid sequence between the variant and NL1 that would result in different epitopes for NL1 and the variant. Additionally, since the fibrinogen domain has no disclosed function, one skilled in the art would not know how to use a polypeptide containing just that domain or a variant thereof. Also, the specification provides no working examples of NL1 binding a TIE receptor. As stated at the beginning of this paragraph, the claims are extremely broad because of the limited structural requirements of the polypeptide and no functional limitations. As stated in the rejection under 35 USC 112, second paragraph, below, the meaning of 90% identity is not clear and so the actual breadth of claim is not clear since two sequence having 90% identity as calculated with one set of parameters could have a significantly lower % identity when calculated with a different set of parameters. Similarly, depending on which amino acid sequence is used as the reference sequence, the claimed polypeptide could be much larger than the fibrinogen domain of NL1. For these reasons, it would require undue experimentation to use the claimed invention.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1 and dependent claims 2-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite because it is unclear what is encompassed by the claim since the specification does not define how "identity" is to be calculated and the art has not recognized one way of calculating identity. The specification says it can be calculated by using the Clustal method of sequence alignment as incorporated into version 1.6 of Lasergene biocomputer software (p. 6, third paragraph). However, this software and the Clustal method of sequence

comparison require input of operator selected parameters, which are absent from the current specification. These parameters include whether gaps are allowed and what "gap weight" is permitted. Further, identity may be calculated relative to the query or matching sequence. These alternative means of calculating are important because they determine what, for example, 90% identity means. Consider two sequences: ACGTAC and ACAC. These can be compared in four ways. The example below illustrates how defining identity can influence the breadth encompassed by the claim. "Query" represents a single sequence being searched. "Match" represents a sequence found which matches the specific query.

match:	ACGTAC	4/6 = 67%	ACGTAC	2/6 = 33%
	| | | |		| |	
query:	AC - - AC	4/4 = 100%	ACAC	2/4 = 50%

Claim 8 is indefinite because it is unclear if the sequence identifier appearing in parentheses after the name of the ligand, *e.g.*, "NL1", is exemplary or limiting. This rejection could be obviated by removal of the parenthesis and addition of a phrase such as "which has the sequence of SEQ ID NO:1", if appropriate.

Claim 14 is indefinite because it recites a polypeptide "fused to a further therapueitc or cytotoxin agent", which implies that there is an initial therapeutic or cytotoxic agent. No such agent is recited in the claim 14 or 8. Elimination of the term "further" would obviate this rejection. (If "further" is deleted in claim 14, it should also be deleted in claim 15.)

Claim 15 is indefinite becuase it is unclear what types of compounds are encompassed by a "member of the vasculare endothelial growth factor (VEGF) family".

Prior Art

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Hanahan (U) describes signaling through TIE1 and TIE2 receptors, and known

ligands for the receptors. Davis et al. (A) describes a nucleic acid encoding TIE-2 ligands (TL1). Davis et al. (B) describes a TIE-2 ligand 2 (TL2) polypeptide. None of these reference teach the currently claimed nucleic acid.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Claire M. Kaufman, whose telephone number is (703) 305-5791. Dr. Kaufman can generally be reached Monday through Friday from 8:00AM to 4:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Stephen Walsh, can be reached at (703) 308-2957.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294. NOTE: If applicant *does* submit a paper by fax, the original signed copy should be retained by the applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office. **Please** advise the examiner at the telephone number above before facsimile transmission.

cmk
June 3, 1998

Stephen Walsh
STEPHEN WALSH
SUPERVISORY PATENT EXAMINER
GROUP 1800